



Understand PFDD Guidance Series and the Impact on Data Submission

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Meet the Speaker

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- The author(s) have no real or apparent conflicts of interest to report.



Agenda

- 1. Increased Emphasis on Patient Voice
- 2. FDA PFDD Methodological Guidance Series
- 3. Guidance: Submitting PRO Data in Cancer Clinical Trials
- 4. Guidance: Submitting Clinical Trial Datasets & Documentation for COA Using IRT

Increased Emphasis on Patient Voice

Increased Emphasis on Patient Voice

- Patients are the experts in the experience of their disease or condition, and they are the ultimate stakeholders in the outcome of medical treatment.
- Robust patient engagement approach is required to collect meaningful patient experience data and incorporate it in the whole drug development lifecycle.
- Increased role and importance of patient experience data in all aspects of healthcare decision making, including drug development strategy from biopharmaceutical organizations, regulatory review and approval process from health authorities, and Health Technology Assessment (HTA) bodies assessment for pricing and reimbursement.



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https://www.fda.gov/patients/evolution-patient-

engagement-fda



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CDER Patient-Focused Drug Development

FDA

1988

Office of AIDS

established

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What is Patient-Focused Drug Development?

Patient-focused drug development (PFDD) is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. As experts in what it is like to live with their condition, patients are uniquely positioned to inform the understanding of the therapeutic context for drug development and evaluation.

The primary goal of patient-focused drug development is to better incorporate the patient's voice in drug development and evaluation, including but not limited to:

- · Facilitating and advancing use of systematic approaches to collecting and utilizing robust and meaningful patient and caregiver input to more consistently inform drug development and regulatory decision-making
- · Encouraging identification and use of approaches and best practices to facilitate patient enrollment and minimizing the burden of patient participation in clinical trials
- · Enhancing understanding and appropriate use of methods to capture information on patient preferences and the potential acceptability of tradeoffs between treatment benefit and risk outcomes
- · Identifying the information that is most important to patients related to treatment benefits, risks, and burden, and how to best communicate the information to support their decision making.



methodological guidance on the

collection of patient experience data, and the use of such data and related

information in drug development.



FDA developed a COA Pilot Grant Program to support the development of publicly available core set(s) of Clinical Outcome Assessments (COAs) and their related endpoints for specific disease indications.



FDA's PFDD meetings have provided

patient advocates, researchers, drug

developers, healthcare providers, and

others, an opportunity to hear the

patient's voice.

key stakeholders, including FDA,



Externally led Patient-Focused Drug Development Meetings

FDA welcomes patient organizations to identify and organize patient-focused collaborations to generate public input on other disease areas.



Condition-Specific Meeting Reports This webpage hosts an alphabetical listing of condition-specific meeting reports and other information related to patients' experience. These meetings include FDA-led Patient-Focused Drug Development (PFDD) meetings, Externally led PFDD meetings, and Patient Listening Sessions.

https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-developmen



Key milestones of EMA interaction with patients and consumers



https://www.ema.europa.eu/en/partners-networks/patients-consumers

Regulatory Science Strategy to 2025

On 31 March 2020, EMA published its Regulatory Science Strategy to 2025 after it was endorsed by EMA's Management Board at its March 2020 meeting.

 EMA Regulatory Science to 2025 - Strategic reflection

 Adopted

 First published: 31/03/2020

 Last updated: 31/03/2020

English (EN) (4.8 MB - PDF)

"Regulatory Science Strategy to 2025" proposes the core recommendation to "Ensure the patient voice is systematically incorporated throughout drug development & associated evidence generation"

Regulatory science strategy | European Medicines Agency (europa.eu)





Home > Regulatory Science/The Science Board/Standard Development > Regulatory Science > Projects Across Multi-Offices in PMDA > Patient Centricity WG

Regulatory Science/The Science Board/Standard Development

Patient Centricity WG

Document

Pharmaceuticals and Medical Devices Agency Guidance on Patient Participation (September 7, 2021) 🥦

Past Presentations (Last 5 years)

 The outlook for Patient involvement in Medical Device Development ~Japanese Regulatory View~ Japan-US HBD East 2021 Think Tank Meeting, Web, January 2022

<u>PMDA's Patient Participation Activities</u>
 18th DIA Japan Annual Meeting 2021, Web, October 2021

Patient Centricity WG | Pharmaceuticals and Medical Devices Agency (pmda.go.jp)





https://www.cde.org.cn/main/news/viewInfoCommon/42c008e28f7004cd19b73949142380bd



BIO Framework for the Use of PED



Framework for the Use of Patient Experience Data Throughout the Product Lifecycle

				inical Developing	FIL			
Current Meeting Opportunities	Critical Path Innovation Meetings	Pre-IND Meetings Other Type A , B, or C Meetings Critical Path Innovation Meetings INTERACT Meetings (CBER)	EoP1 Meetings EoP2 Meetings Pre-NDA/BLA Meetings Other Type A, B, or C Meetings Other Type A, B, or C Meetings Other Type A, Other Type A, B		Mid-cycle Communication Late Cycle Meetings Advisory Committee Meetings	Other Type B or C Meetings		
Product Stage	Research & Discovery	Preclinical Development	Phase I	Phase 2	Phase 3	Health Authority Review and Marketing Authorization	Postmarketing	
Examples of Patient Experience Data Applicable to the Product Lifecycle	 Experience on current treatments Unmet medical need Disease familiarization 	 Treatment burden Patient input on protocol designs Clinical trial burden Disease burden Natural history study Identification of clinical outcome assessments 	 Patient benefit- Treatment burd Patient input or Clinical trial but Disease burder Natural history 	n protocol designs rden 1 study cal outcome assessn	nents	Patient risk tolerance Clinical outcome assessments	 Patient outcome in clinical practice Clinical outcome assessments Development of patient support applications 	
Relevant Decisions made During this Phase of the Product Lifecycle	Product design adaptation	 Product design (i.e., type of device, how to take the medicine, etc.) Protocol design (i.e. meaningful endpoints) Clinical trial participation Understanding the feasibility of trial participation 	 Clinical trial de Personalized m To inform the c 	identification sessment ne Assessment Ident		 Structured benefit-risk assessment Subpopulation identification Labeling optimization Discussion at Advisory Committee meetings Labeling 	Label/indication expansion Shared decision making Personalized medicine/ biomarkers Quality of care/adherence (i.e., label clarification, physician counseling) Risk management Value frameworks	

Clinical Development

FDA PFDD Methodological Guidance Series

Background

- Patient Focused Drug Development (PFDD) is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.
- Legislation is driving PFDD and increased, transparent use of Patient Experience Data in US. <2012 (Prescription Drug User Fee Act <u>PDUFA V</u>), 2017 (<u>PDUFA VI</u>), and 2022 (<u>PDUFA VII</u>), 2016 (<u>21st Century Cures Act</u>)>
- The series of PFDD guidance documents are part of FDA's efforts in accordance with the legislation requirements to facilitate the incorporation of patient experience data into medical product development.

C+TMFInterch

Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry, Food and Drug

Administration Staff, and Other Stakeholders Patient-Focused Drug Development: Methods to Identify What Is Important to Patients Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this dard document should be unbunited within 90 days of publication in the *Faderal Register* of the notice nanouscitud flex availability of the dard guidance. Subant electronic comments to <u>Inter/www retraintons</u> ages, Subant written comments to the Dockets Management Start (FRFA-305). Food and Durg Administration, 500 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket sumbristication envices of availability that publication. Inter *Federal Register*.

For exercises regarding this dard document, context (CDEE) Office of Communications, Drivision of Drug Hofmannion at dynamic Diff da has per, 35-34-374 of 31-37-340, 01-(CBER) Office of Communication. Observation and Development at good/fif da have per, 80-432 drive of 240-42, bit of the data and the data and the data and the data and the for Devices and Rabid per (11-11-11) data and grade to 1, per horizon and the data and the data and the data and the data and the horizon and the data and the data and the data and the data and the horizon and the data and the data and the data and the data and the horizon and the data and the data and the data and the data and the horizon and the data and the data and the data and the data and the horizon and the data and the data and the data and the data and the horizon and the data and

Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Center for Desices and Radiological Health (CDRH)

> June 2022 Procedural

Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only

Comments and suggestions regarding this draft document should be robusited within <u>drafts</u> of publication in the *Polentil Registre* of the solice annuament per variability of the draft publication. Submit electronic comments to <u>they solver resultings</u> approx. Submit written comments to the Detect Management SMIT (DFA 5-05), submit written beckets mumbel und in the socie of early analytications the *Polenti* Arguerer.

For questions regarding this draft document, contact (CDER) Office of Communications, Division of Drug Information at <u>drapinfo/Bfda lbbs gov</u>, 855-543-3784, or 301-796-3400 or (CBER) Office of Communication, Outrach and Development, 800-885-4700 or 246-402-8014 (CDBER) Detailed Science and Brancingers Devenue (CDBER) Development, 800-885-4700, or 246-402-8014



April 2023 Procedura



lune 2020 rocedural



U.S. Department of neutra and numan services Food and Drug Administration Center for Drug Evaluation and Research (CDER) enter for Biologics Evaluation and Research (CBER) February 2022

FDA PFDD Guidance



Collecting Comprehensive and Representative Input

Overview of methods to collect robust, meaningful, and sufficiently representative patient input to inform medical product development and regulatory decision-making. Serve only as a basis for dialogue in the evolving and growing discipline of the science of patient input.



Patient-Focused Drug Development: Methods to Identify What Is Important to Patients Approaches to identifying what is most important to patients with respect to their experience as it relates to burden of disease/condition and burden of treatment



Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

Recommended approaches to selecting, modifying, developing, and validating fit-for-purpose clinical outcome assessments (COAs) to measure outcomes of importance to patients in clinical trials.



Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making Methods, standards, and technologies for collecting and analyzing COA data for regulatory decision-making, including selecting the COA-based endpoint and determining clinically meaningful change in that endpoint.



Technical Specifications Guidance as Supplement

To supplement the PFDD Guidance Series, FDA issued two technical specifications guidance documents to provides specifications for submission of the standardized dataset content and structure of SDTM and ADaM datasets and specifications for recommended tables and figures.

Submitting Patient-Reported Outcome Data in Cancer Clinical Trials

Guidance for Industry Technical Specifications Document

For questions regarding this technical specifications document, contact CDER at <u>cder-edata@fda.hhs.gov</u>.

Nov 2023

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Oncology Center of Excellence (OCE)

> November 2023 Technical Specifications Document

Submitting Clinical Trial Datasets and Documentation for Clinical Outcome Assessments Using Item Response Theory

> **Guidance for Industry** Technical Specifications Document

> > Nov 2023

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

> U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER)

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November 2023 Technical Specifications Document

Guidance: Submitting PRO Data in Cancer Clinical Trials

SDTM ADaM Tables&Figures

SDTM

QS Domain

Additional information to be considered in SUPPQS

SUPPQS Considerations	NSV for Reference
Data Collection Mode	ADMODP (Administration Mode of Presentation)
Language	DCLANG (Data Collection Language)
	COLAID (Collected Administrator Identifier)
	COLRID (Collected Respondent Identifier)
	COLRRL (Collected Respondent Relationship)
Data Collector	PPRAID (Preprinted Administrator Identifier)
	PPRRID (Preprinted Respondent Identifier)
	PPRRRI (Preprinted Respondent Relationship ID)

Could be included in QX (or ZQ ?) domain which is under discussion by CDISC

Missing data handling

-Different scenarios and suggested QSREASND terms.

-If PRO measurement is missed, normally each missing item and summary score shall be included

-Do not create data for unadministered items due to the use of computerized adaptive testing (CAT)

TS Domain

- TSPARAMCD = 'FDATCHSP'
- TSPARAM = 'FDA Tech Spec'
- TSVAL = 'Oncology PROs Technical Specifications Guidance v1.0'

cdisc

ADaM

Possible match between SDTM.QS and ADQS

SDTM Variable	ADaM Variable
QSTESTCD	PARAMCD
QSTEST	PARAM
QSCAT	PARCAT1
QSSCAT	PARCAT2
QSSTRESN (quant.)	AVAL
QSSTRESC(qual.)	AVALC

- Following ADaM Basic Data Structure, support needs of ٠ analysis and keep traceability.
- Dataset name could be ADQS and use PARCAT1 to differentiate different instruments if multiple instruments exist.
- All individual item scores and summary scores shall be contained.

More scei	narios of F	PARCATy u	sage		PARCAT1		PARCAT2	PARCAT3	PARAM	
P/	PARCAT1	PARCAT2	PARCAT3	PARC	AT4 PARCAT5	PARA	M nptom 1	Attribute 1	Symptom 1 Attr	ibute 1
Measure N	Measure Name and Version	ITEM	Subscale Score 1	Scale Se	ore A Scale Score B	Ttem 1	unitom 2	Attribute ?	Sumntom 2 Attr	ibute ?
Measure N	Measure Name	ITEM	Subscale	Scale §	PARCATI		PARCAT2	PARCAT3	PARCAT4	PARAM
Measure N	and Version	TTEM	Score 1	Scale :	Measure Name and	Version	ITEM	Subscale Score	e 1 Scale Score A	Item 1
	Measure Name and Version	ITEM	Subscale Score 1	Scale §	Measure Name and	Version	ITEM	Subscale Score	e 1 Scale Score A	Item 2
Ρ.	Measure Name	ITEM	Subscale	Scale §	Measure Name and	Version	ITEM	Subscale Score		Item 3
Measure 1	and Version Measure Name		Score 2 Subscale		Measure Name and	Version	ITEM	Subscale Score	e 2 Scale Score A	Item 4
Measure 1	and Version	ITEM	Score 2	Scale S	Measure Name and	Version	ITEM	Subscale Score	e 2 Scale Score A	Item 5
Measure 1	Measure Name and Version	ITEM	Subscale Score 3	Scale 5	Measure Name and	Version	ITEM	Subscale Score	e 3 Scale Score B	Item 6
Measure 1	Measure Name	SUBSCALE	Subscale	Scale §	Measure Name and	Version	SUBSCALE SCORE	E Subscale Score	e 1 Scale Score A	Subscale Score 1
Measure 1	and Version	SCORE	Score 1	Scale :	Measure Name and	Version	SUBSCALE SCORE	Subscale Score	e 2 Scale Score A	Subscale Score 2
Measure 1	Measure Name and Version	SUBSCALE SCORE	Subscale Score 2	Scale 5	Measure Name and	Version	SUBSCALE SCORE	Subscale Score	e 3 Scale Score B	Subscale Score 3
Measure 1	Measure Name	SUBSCALE	Subscale	Scale 5	Measure Name and	Version	SCALE SCORE		Scale Score A	Scale Score A
Measure 1	and Version	SCORE	Score 3	Jeane .	Measure Name and	Version	SCALE SCORE		Scale Score B	Scale Score B
Measure 1	Measure Name and Version	SCALE SCORE		Scale S	Men	Scare Sco	"	•	•	,;
COISC	Measure Name and Version	SCALE SCORE			Scale Score B	Scale Sco	re B taClearImpac	t		18

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ADaM (cont.)

Represent missing PRO Data

- Copying from the SDTM QS.QSSTAT = 'NOT DONE' and corresponding QS.QSREASND
- When not exist in SDTM QS dataset and required in ADQS, derive new phantom records with DTYPE = 'PHANTOM', QS.QSSTAT and QS.QSREASND both null, ADQS.AREASND could be derived for the reason not done if applicable.

PROEXPFL and PROSCMFL (Y or null)

PROEXPFL (PRO Expected Flag)	PROSCMFL(PRO Score Completed Flag)					
 An indicator variable to specify whether the PRO parameter (e.g., the individual item or summary score reported within a row) corresponds to a planned (per protocol) PRO assessment timepoint. If PRO objectives for both (1) clinical benefit and (2) safety and tolerability are present within the same trial, two PRO Expected Flag variables should be submitted within the ADQS dataset (e.g., PROEX1FL and PROEX2FL) with definitions for each variable 	 An indicator variable to specify whether the PRO item score or summary score is populated at a planned (per protocol) PRO assessment timepoint (i.e., where AVAL or AVALC is not empty/null). 					





Estimands Intercurrent Events handling in ADQS

Intercurrent Events: events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. Intercurrent events should be addressed when describing the clinical question of interest to precisely define the treatment effect that is to be estimated.

PRO to Evaluate Clinical Benefit	PRO to Inform Safety and Tolerability
 ADQS records should be created for all randomized (including randomized but not treated) patients, even after intercurrent event (treatment discontinuation, death, etc.) if there is PRO measure originally planned. Phantom records should be created if no records in SDTM.QS. 	 ADQS records are mainly from period before treatment discontinuation. PRO measure after treatment discontinuation should be minimized to reduce patient burden. It is not required to create Phantom records for assessment timepoints after a patient's death or for any timepoints for randomized but not treated patients.



ADaM (cont.)

Total Score calculated in ADQS only

AVALC is not included as standard results in quantitative

THE PROPERTY AND			DIDGITI											
USUBJID		AVISIT	PARCAT1	PARAM		AVAL	QSSTAT	QSREASND	DTYPE	AREASND	DCTREAS	PROEXPFL	PROSCMFL	ONTRTFL
A_100_1	SCREENING	SCREENING	Measure Name and Version		I01	3						Y	Y	
A_100_1	SCREENING	SCREENING	Measure Name and Version	I01-Item 2	I02	5						Y	Y	
A_100_1	SCREENING	SCREENING	Measure Name and Version	Total Score	TS	8						Y	Y	
A_100_1	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 1	I01		NOT DONE]	Y		Y
A_100_1	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 2	I02	4						Y	Y	Y
A_100_1	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	Total Score	TS					NOT CALCULABLE		Y		Y
A_100_1	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 1	I01	2		Ī				Y	Y	Y
A_100_1	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 2	I02	4						Y	Y	Y
A_100_1	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	Total Score	TS	6						Y	Y	Y
A_100_1	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 1	I01		NOT DONE	PATIENT REFUSAL		PATIENT REFUSAL	1	1	1	- 1
A_100_1	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 2	I02		NOT DONE	PATIENT REFUSAL		PATIENT REFUSAL	Phanto	om recor	ds creat	ed for tir
A_100_1	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	Total Score	TS					PATIENT REFUSAL			ath, AV	
A_100_2	SCREENING	SCREENING	Measure Name and Version	I01-Item 1	I01	4			1					
A_100_2	SCREENING	SCREENING	Measure Name and Version	I01-Item 2	I02	5					QSRE	ASND, F	PROEXP	FL, PRO
A_100_2	SCREENING	SCREENING	Measure Name and Version	Total Score	TS	9					and O	NTRTEI	are all r	sull.
A 100 2	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 1	I01		NOT DONE	HOSPITALIZATION		HOSPITALIZATION				iun
A_100_2	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 2	I02		NOT DONE	HOSPITALIZATION		HOSPITALIZATION		Y		
A_100_2	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	Total Score	TS					HOSPITALIZATION		Y		
A 100 2	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 1	I01				PHANTOM	DEATH	DEATH			
A 100 2	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 2	102				PHANTOM	DEATH	DEATH			
A 100 2	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	Total Score	TS		-		PHANTOM	DEATH	DEATH			
A 100 2	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 1	I01		-		PHANTOM	DEATH	DEATH			
A 100 2	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version		102		-		PHANTOM	DEATH	DEATH			
A 100 2			Measure Name and Version						PHANTOM	DEATH	DEATH			
<u></u>				- star score			·	l		******			1	

PROEXPFL Considerations

- Expected assessment timepoint per protocol, on therapy or at paused treatment (PROEXPFL=Y)
- Translation of the PRO measure is not available in the patient's language (PROEXPFL=null)
- PRO assessment timepoints after patient death (PROEXPFL=null)
- Patients who discontinued from treatment for reason other then death (PROEXPFL=Y for clinical benefit case. Measurement should be minimized after treatment discontinuation for safety/tolerability case)
- Patients who were randomized but not treated (PROEXPFL=Y for clinical benefit case, PROEXPFL=null for safety/tolerability case)



Table and Figures – patient disposition

Clinical benefit

Table A4. Patient Disposition when Evaluating Clinical Benefit (Denominator = Randomized Population)¹

	Treatment Arm	Randomized Patients (N)	PRO Expected ²							
Analysis Visit			Patients On Therapy, n (%)	Treatment Discontinuation: Disease Progression, n (%)	Treatment Discontinuation: Adverse Event (AE), n (%)	Treatment Discontinuation: Other Reasons, n (%)				
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Π			
Basenne	Treatment	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	Π			
Cycle 2	Control	600	564 (94.0%)	16 (2.7%)	15 (2.5%)	0 (0.0%)	Π			
Day 1	Treatment	602	572 (95.0%)	10 (1.7%)	13 (2.2%)	0 (0.0%)				
Cycle 3	Control	600	525 (87.5%)	30 (5.0%)	26 (4.3%)	6 (1.0%)	Π			
Day 1	Treatment	602	542 (90.0%)	23 (3.8%)	21 (3.5%)	0 (0.0%)	Π			



Figure A1. Patient Disposition when Evaluating Clinical Benefit (Denominator = Randomized Population)

Safety and tolerability

Table A5. Patient Disposition when Informing the Evaluation of Safety and Tolerability (Deno

						PI	RO Not
Analysis Visit	Treatment Arm	Randomized Population (N)	Safety Population (N)	PRO Expected, ⁵ n (%)	Death, n (%)	Treatment Discontinuation: Disease Progression, n (%)	Ti Disco ↓ Eve
Baseline	Control	600	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0
Baseline	Treatment	602	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0
Cycle 2	Control	600	600	564 (94.0%)	5 (0.8%)	16 (2.7%)	1:
Day 1	Treatment	602	602	572 (95.0%)	7 (1.2%)	10 (1.7%)	19
Cycle 3	Control	600	600	525 (87.5%)	13 (2.2%)	30 (5.0%)	20
Day 1	Treatment	602	602	542 (90.0%)	16 (2.7%)	23 (3.8%)	21



Treatment Discontinuation: Other Reasons (PRO Not Expected)

= Treatment Discontinuation: Adverse Event (PRO Not Expected)

2024 Europe CDISC+TMF

Table and Figures – available data rate & completion rate

Clinical benefit

Table A6. Available Data Rate for Clinical Benefit (Denominator = Randomized Population)7

					Reason for PRO Not Completed,9 n (%)							
Analysis Visit	Treatment Arm	Randomized Patients (N)	PRO Completed, n (%)	PRO Not Completed ⁸ (excluding Death), n (%)	Patient Unable to Complete due to Disease Progression	Patient Unable to Complete due to Adverse Event (AE)	Patient Refusal	Device Failure	Reason Unknown, ¹⁰ n (%)			
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Basenne	Treatment	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Cycle 2	Control	600	556 (92.7%)	39 (6.5%)	8 (1.3%)	25 (4.2%)	6 (1.0%)	0 (0.0%)	0 (0.0%)			
Day 1	Treatment	602	551 (91.5%)	44 (7.3%)	3 (0.5%)	36 (6.0%)	5 (0.8%)	0 (0.0%)	0 (0.0%)			
Cycle 3	Control	600	542 (90.3%)	45 (7.5%)	14 (2.3%)	26 (4.3%)	0 (0.0%)	5 (0.8%)	0 (0.0%)			
Day 1	Treatment	602	539 (89.5%)	47 (7.8%)	10 (1.7%)	32 (5.3%)	5 (0.8%)	0 (0.0%)	0 (0.0%)			

Index Cycl. Dayl Cycl. Dayl</

Centrol N = 600 Treatm ent N = 602

Figure A3. Available Data Rate for Clinical Benefit (Denominator = Randomized Population)

PROEXPFL = 'Y' and PROSCMFL=""

PRO Not Completed: Patient Unable to Complete due to Disease Pro-

Control N = 600 Treatment N = 602

Figure A4. Completion Rate for Safety and Tolerability (Denominator = PRO Expected Population)

Treatment N = 602

Centrol N = 600

PRO Completed



Table A7. Con	npletion Ra	te for Safety a	and Tolerability (I	Denominator = P	RO Expected	Population) ¹¹				
					Reason for PRO Not Completed, ¹³ n (%)					
Analysis Visit	Treatment Arm	PRO Expected ¹² (N)	PRO Completed, n (%)	PRO Not Completed, n (%)	Patient Refusal	Patient Unable to Complete due to AE	Device Failure	Reason Unknown, ¹⁴ n (%)		
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Basennie	Treatment	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Cycle 2 Day 1	Control	564	542 (96.1%)	22 (3.9%)	6 (1.1%)	16 (2.8%)	0 (0.0%)	0 (0.0%)		
Cycle 2 Day 1	Treatment	572	536 (93.7%)	36 (6.3%)	5 (0.9%)	31 (5.4%)	0 (0.0%)	0 (0.0%)		
Crude 2 Day 1	Control	525	510 (97.1%)	15 (2.9%)	0 (0.0%)	10 (1.9%)	5 (1.0%)	0 (0.0%)		
Cycle 3 Day 1	Treatment	542	516 (95.2%)	26 (4.8%)	5 (0.9%)	21 (3.9%)	0 (0.0%)	0 (0.0%)		





Table and Figures – distribution

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Table A8. Distribution of Categorical Responses for Item 1 (Safety and Tolerability Example)¹⁵

ſ	Amelania Trinit	Transforment Arms	PRO	PRO	PRO Not		Response
	Analysis Visit	Treatment Arm	Expected ¹⁶	Completed, n (%)	Completed, n (%)	Not at all	A litt
	Develope	Control	600	600 (100.0%)	0 (0.0%)	332 (55.3%)	220 (36.
	Baseline	Treatment	602	602 (100.0%)	0 (0.0%)	313 (52.0%)	228 (37.
	a 1 a 5 d	Control	564	542 (96.1%)	22 (3.9%)	299 (55.2%)	188 (34.
	Cycle 2 Day 1	Treatment	572	536 (93.7%)	36 (6.3%)	268 (50.0%)	199 (37.
	Crude 2 Day 1	Control	525	510 (97.1%)	15 (2.9%)	225 (44.1%)	189 (37.
	Cycle 3 Day 1	Treatment	542	516 (95.2%)	26 (4.8%)	203 (39.3%)	193 (37.

Table A9. Summary Statistics for Item 2 with Continuous Response Options (Safety and Tolerability Example)¹⁸

Analysis Visit		Control	Treatment					
	PRO Expected ¹⁹ (N)	600	602					
Baseline	PRO Not Completed, n (%)	0 (0.0%)	0 (0.0%)					
	PRO Completed, n (%)	600 (100.0%)	602 (100.0%)					
	Summary Statistics ²⁰							
	Mean	2.1	1.0					
	Standard Deviation	1.8	0.9					
	Standard Error	0.07	0.04					
	Median	2.1	1.0					
	Minimum	0.0	0.0					
	Maximum	4.1	2.0					
	PRO Expected (N)	564	572					
	PRO Not Completed, n (%)	22 (3.9%)	36 (6.3%)					
	PRO Completed, n (%)	542 (96.1%)	536 (93.7%)					
	Summary Statistics							
Cycle 2 Day 1	Mean	7.1	5.1					
	Standard Deviation	4.6	3.7					
	Standard Error	0.19	0.15					
	Median	7.2	5.1					
	Minimum	0.3	0.2					
	Maximum	11.8	9.8					
	PRO Expected (N)	525	542					
	PRO Not Completed, n (%)	15 (2.9%)	26 (4.8%)					
	PRO Completed, n (%)	510 (97.1%)	516 (95.2%)					
	Summary Statistics							
Cycle 3 Day 1	Mean	6.2	3.9					
	Standard Deviation	5.2	2.7					
	Standard Error	0.23	0.12					
	Median	6.6	3.8					
	Minimum	0.1	0.0					

Figure A5. Distribution of Categorical Responses for Item 1 (Safety and Tolerability Example where Denominator = PRO Completed)



Figure A6. Descriptive Means for Item 2 with Continuous Response Options (Safety and Tolerability Example for Physical Functioning)21,22



Table and Figures – distribution of change

Figure A7. Distribution of Change in Response Categories from Baseline for Item 1 (Safety and Tolerability Example where



Table A10. Distribution of Change in Response Categories from Baseline for Item 1 (Safety and Tolerability Example

Analyzia	Turneturent	PRO	PRO	PRO Not								
Analysis Visit		Expected ²⁴	Completed, n (%)	Completed, n (%)	Improving 1	Improving 2	Improving 3	No Change		Worsening 2		
Cycle 2	Control	564	542 (96.1%)	22 (3.9%)	38 (7.0%)	11 (2.0%)	3 (0.6%)	303 (55.9%)	132 (24.4%)	38 (7.0%)		
Day 1	Treatment	572	536 (93.7%)	36 (6.3%)	33 (6.2%)	14 (2.6%)	6 (1.1%)	296 (55.2%)	141 (26.3%)	32 (6.0%)		
Cycle 3	Control	525	510 (97.1%)	15 (2.9%)	50 (9.8%)	24 (4.7%)	10 (2.0%)	261 (51.2%)	126 (24.7%)	29 (5.7%)		
Day 1	Treatment	542	516 (95.2%)	26 (4.8%)	44 (8.5%)	28 (5.4%)	11 (2.1%)	261 (50.6%)	123 (23.8%)	39 (7.6%)		

Table A11. Change from Baseline for Item 2 with Continuous Response Options (Safety and Tolerability Example)²⁶

Analysis Visit		Treatment	Control
	PRO Expected ²⁷ (N)	564	572
	PRO Not Completed, n (%)	22 (3.9%)	36 (6.3%)
	PRO Completed, n (%)	542 (96.1%)	536 (93.7%)
	Summary Statistics ²⁸		
Cuelo 2 Dev 1	Mean	4.9	4.5
Cycle 2 Day 1	Standard Deviation	4.0	1.7
	Standard Error	0.17	0.19
	Median	5.0	4.2
	Minimum	-1.1	-1.3
	Maximum	10.3	9.0
	PRO Expected ¹ (N)	525	542
	PRO Not Completed, n (%)	15 (2.9%)	26 (4.8%)
	PRO Completed, n (%)	510 (97.1%)	516 (95.2%)
	Summary Statistics		
Cycle 3 Day 1	Mean	4.1	2.9
Cycle 5 Day 1	Standard Deviation	5.7	5.6
	Standard Error	0.25	0.24
	Median	4.2	2.9
	Minimum	-1.6	-1.4
	Maximum	8.0	8.5

Figure A8. Change from Baseline for Item 2 with Continuous Response Options (Safety and Tolerability Example)^{29 30}





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Table and Figures – healthcare utilization

5.3.7 Incidence of Healthcare Utilization

Table A12. Incidence of Healthcare Utilization (Safety and Tolerability Example where Denominator = PRO Expected)³¹

					Heal	thcare Utiliz	ation Intervention, n	(%)	
Analysis Visit	Treatment Arm	Randomized Patients	PRO Expected ³² (N)	Emergency Department (ED) Visits	Hospitalizations	Opiates	Supportive Care Medications (e.g., Steroids, Transfusions, Growth Factors)	Supportive Care Procedures (e.g., Palliative: Hospice, Nephrostomy)	Other (Describe)
Baseline	Control	600	600	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Basenne	Treatment	602	602	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day	Control	600	564	5 (0.9%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	3 (0.5%)	0 (0.0%)
1	Treatment	602	572	5 (0.9%)	3 (0.5%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Cycle 3 Day	Control	600	525	7 (1.3%)	5 (1.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	0 (0.0%)
1	Treatment	602	542	7 (1.3%)	3 (0.6%)	0 (0.0%)	2 (0.4%)	5 (0.9%)	0 (0.0%)



Guidance: Submitting Clinical Trial Datasets & Documentation for COA Using IRT

Item Response Theory (IRT)

IRT-based Computerized Adaptive Testing (CAT)

Scope and Background

- □ Fixed-form COAs that are developed and/or scored using Item Response Theory (IRT)
- COAs administered using IRT-based Computerized Adaptive Testing (CAT)

•	IRT	IRT-based CAT
	 Statistical framework used to model the relationship between latent traits (unobservable characteristics or attributes) and responses to items on a test or questionnaire. IRT can be used to develop, evaluate, and score COA measures. It provides a way to estimate the level of a latent trait based on a person's responses to a set of items. Item parameters typically include: <u>Difficulty parameter:</u> the level of the latent trait where a respondent has a 50% chance of endorsing the item (or in the case of polytomous models, of endorsing a particular response category or higher). 	A sequential form of individual testing administered by a computer in which successive items in the COA measure are selected for administration based primarily on the item's psychometric properties and content in relation to the patient's responses to previous items, to provide individualized testing for a person. Selection is based on the likelihood that
	 <u>Discrimination parameter:</u> how well the item differentiates between individuals at different levels of the latent trait. <u>Other</u>: for example, item loading parameters for item with continuous response options 	an item will be helpful in improving the estimate of the person's score, not on the relevance of the item content.

Specific Information Required

When IRT is used for scoring

- Scoring details, including methods for generating scores (e.g., latent factor score (referred to as theta score throughout this document), scaled score)
- Conversion table(s) used to convert a theta score to other transformed scores (e.g., T-score), if applicable
- Psychometric software (e.g., the software name and version)

When COAs administered using CAT

- Details of item selection or routing algorithm (e.g., the algorithm used to select the next item or sets of items for the patient with content constraints and/or item exposure control (if applicable))
- The starting criteria with justification
- The termination criteria (i.e., the stopping rule) with justification



SDTM

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Domain	Recommendations
ZQ - similar concept with QX domain which is under discussion by CDISC for SDTMIG 4.0	 Item dataset to represent for the item bank: all items, response options, and associated model parameters when IRT is only used in scoring, the ZQ dataset should contain information for all items within the fixed/static COA Domain for QRS reference, including RDOMAIN, both ZQTEST/CD and ZQPARM/CD, ZQVALN/C, and ZQSE(standard error)
QS, FT, RS	 REFID could be used for covered COA measures that use CAT, since item selection and/or the order of item administration from the item bank can vary by patient and/or by assessment timepoint. Recommended value forREASND at different scenarios. ALL can be used asTESTCD when COA measure using CAT and the measure is not administered. Unadministered items due to the use of Computerized Adaptive Testing within the item bank should not be included within the QS dataset. Additional variables in SUPP: Data Collection Mode, Data Collector, Language, Response Time
TS	 TSPARAMCD = 'FDATCHSP' TSPARAM = 'FDA Tech Spec' TSVAL = 'IRT-Based COAs Technical Specifications Guidance v1.0'



SDTM – ZQ example

EIB01-Item 1 has 5 response items:

• 5-1=4 threshold parameters

• 1 item slop parameter

All possible numeric and/or character response values for items, minimum/maximum and explanation

•	STUDYID	DOMAIN	RDOMAIN	ZQSEQ	ZQCAT	ZQTEST	ZQTESTCD	ZQPARMCD	ZQPARM	ZQVALN	ZQVALC	ZQSE
	StudyA	ZQ	QS	1	Example Item Bank v.1.0	EIB01-Item 1	EIB01	RESP	Item Response	1	Never	
	StudyA	ZQ	QS	2	Example Item Bank v.1.0	EIB01-Item 1	EIB01	RESP	Item Response	2	Rarely	
	StudyA	ZQ	QS	3	Example Item Bank v.1.0	EIB01-Item 1	EIB01	RESP	Item Response	3	Sometimes	
	StudyA	ZQ	QS	4	Example Item Bank v.1.0	EIB01-Item 1	EIB01	RESP	Item Response	4	Often	
•	StudyA	ZQ	QS	5	Example Item Bank v.1.0	EIB01-Item 1	EIB01	RESP	Item Response	5	Always	
10	StudyA	ZQ	QS	6	Example Item Bank v.1.0	EIB01-Item 1	EIB01	TPAR	Threshold Parameter	-1.2		0.29
•	StudyA	ZQ	QS	7	Example Item Bank v.1.0	EIB01-Item 1	EIB01	TPAR	Threshold Parameter	-0.6		0.14
	StudyA	ZQ	QS	8	Example Item Bank v.1.0	EIB01-Item 1	EIB01	TPAR	Threshold Parameter	0.1		0.02
.	StudyA	ZQ	QS	9	Example Item Bank v.1.0	EIB01-Item 1	EIB01	TPAR	Threshold Parameter	0.8		0.13
1.1	StudyA	ZQ	QS	10	Example Item Bank v.1.0	EIB01-Item 1	EIB01	SLOPE	Item Slope	2.0		0.22

Item Slope:

Discrimination parameter, is a measure of how well an item can differentiate between individuals with different levels of the latent trait.

Threshold Parameter:

Difficulty parameters, are used in IRT models to indicate the point on the latent trait scale at which a respondent has a 50% chance of responding at or above a certain category. The parameters could be different in different IRT models

ADaM

- Should contain all individual items and summary scores (e.g., raw score, theta score, scale score (e.g., a standardized score such as T-score)) and associated standard errors.
- For CAT, additional information such as the number of items that were scored (i.e., scored count) and the number of items to which the patient responded (i.e., total item count) should be submitted to validate that the termination criteria for the CAT was met and that theta score was not calculated prematurely.

••••	USUBJID	AVISIT	PARCAT1	PARAM	PARAMCD	AVAL	QSSEQ	VISIT	DTYPE	QSSTAT	QSREASND
	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB01-Item 1	EIB01	4	1	VISIT 1			
	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB03-Item 3	EIB03		2	VISIT 1		NOT DONE	RESPONSE NOT PROVIDED
	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB04-Item 4	EIB04	4	3	VISIT 1			
	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB05-Item 5	EIB05	5	4	VISIT 1			
	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB07-Item 7	EIB07	3	5	VISIT 1			
i	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-Raw Score	EIBRAW	12		VISIT 1			
	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-Theta Score	EIBTHETA	2		VISIT 1			
1	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-T-Score	EIBTSCR	70		VISIT 1			
	A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-Standard Error	EIBSE	1.8		VISIT 1			
	A_100_1001	VISIT 2	Example Item Bank v.1.0	All Questions	QSALL		6	VISIT 2		NOT DONE	STUDY SITE FAILED TO ADMINISTER
••;•	A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-Raw Score	EIBRAW			VISIT 2	PHANTOM		
1.	A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-Theta Score	EIBTHETA			VISIT 2	PHANTOM		
	A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-T-Score	EIBTSCR			VISIT 2	PHANTOM		
	A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-Standard Error	EIBSE			VISIT 2	PHANTOM		
	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB01-Item 1	EIB01	2	7	VISIT 3			
	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB05-Item 5	EIB05	1	8	VISIT 3			
	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB08-Item 8	EIB08	1	9	VISIT 3			
1	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-Raw Score	EIBRAW	16		VISIT 3			
S-01-5	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-Theta Score	EIBTHETA	2.5		VISIT 3			
••••	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-T-Score	EIBTSCR	75		VISIT 3			
· · ·	A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-Standard Error	EIBSE	3.2		VISIT 3			





Thank You!

